Efavirenz (EFV, Sustiva)

For additional information see Drugs@FDA:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Capsules: 50 mg and 200 mg

Tablets: 600 mg

Combination Tablets:

- *With emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF):*
  EFV 600 mg + FTC 200 mg + TDF 300 mg (Atripla)

Dosing Recommendations

Neonate/infant dose:

EFV is not approved for use in neonates/infants.

Pediatric dose:

Children <3 years of age:
No data are currently available on the appropriate EFV dosage for children <3 years of age.

Children ≥3 years and body weight ≥10 kg:
Administer EFV once daily:

Weight (kg)	EFV Dose (mg)*†
10 to <15	200
15 to <20	250
20 to <25	300
25 to <32.5	350
32.5 to <40	400
≥40	600

* The dose in mg can be dispensed in any combination of capsule strengths.

† Some experts recommend a dose of 367 mg/m^2 of body surface area (maximum dose of 600 mg) because of concern for underdosing, especially at the upper end of each weight band (see Pediatric Use for details).

Adolescent (body weight ≥40 kg)/adult dose:

600 mg once daily.

Atripla (EFV + FTC + TDF)
Atripla should not be used in pediatric patients

Selected Adverse Events

- Rash
- Central nervous system (CNS) symptoms such as dizziness, somnolence, insomnia, abnormal dreams, impaired concentration, psychosis, seizures
- Increased transaminases
- False-positive with some cannabinoid and benzodiazepine tests
- Teratogenic
- Lipohypertrophy although a causal relationship has not been established and this adverse event may be less likely than with the boosted protease inhibitors (PIs)

Special Instructions

- Administer EFV on an empty stomach, preferably at bedtime. Avoid administration with a high-fat meal because of potential for increased absorption.
- Administer Atripla on an empty stomach.
- Bedtime dosing is recommended, particularly during the first 2 to 4 weeks of therapy, to improve tolerability of CNS side effects.
- EFV should be used with caution in adolescent women of childbearing age because of the risk of teratogenicity.

Metabolism

- Cytochrome P450 3A4 (CYP3A4) inducer/inhibitor (more inducer than inhibitor).
- CYP3A4 and CYP2B6 substrate.
- **Dosing of EFV in patients with hepatic im-**

<40 kg where the EFV dose would be excessive.
Adult dose: One tablet once daily.

EFV in combination with other antiretroviral (ARV) drugs:
Dosage adjustment or the addition of ritonavir (RTV) may be necessary when EFV is used in combination with atazanavir (ATV), fosamprenavir (FPV), indinavir (IDV), lopinavir/ritonavir (LPV/r), or maraviroc (MVC).

pairment: No recommendation is currently available; use with caution in patients with hepatic impairment.

- **Adult dose of Atripla in patients with renal impairment:** Because Atripla is a fixed-dose combination product, it should not be used in patients with creatinine clearance (CrCl) of <50 mL/minute or in patients on dialysis.
- Interpatient variability in EFV exposure can be explained in part by polymorphisms in CYP450 with slower metabolizers having higher risk of toxicity. (See Pediatric Use for information about therapeutic drug monitoring [TDM] for management of mild or moderate toxicity.)

Drug Interactions (See also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.)***:***

- *Metabolism:* Mixed inducer/inhibitor of CYP3A4 enzymes; concentrations of concomitant drugs can be increased or decreased depending on the specific enzyme pathway involved. There are multiple drug interactions with efavirenz.
- Before efavirenz is administrated, the patient's medication profile should be carefully reviewed for potential drug interactions with efavirenz.

Major Toxicities:

- *More common:* Skin rash, increased transaminase levels. CNS abnormalities, such as dizziness, somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, euphoria, seizures, primarily reported in adults.
- *Rare:* Prenatal efavirenz exposure has been associated with CNS congenital abnormalities in the offspring of cynomolgus monkeys. Based on these data and retrospective reports in humans of an unusual pattern of severe CNS defects in five infants after first-trimester exposure to efavirenz-containing regimens (three meningomyelocoeles and two Dandy-Walker malformations), efavirenz has been classified as Food and Drug Administration (FDA) Pregnancy Class D (positive evidence of human fetal risk). Efavirenz use in the first trimester of pregnancy should be avoided. Women of childbearing age should undergo pregnancy testing and be counseled about the risks associated with fetal exposure to efavirenz and the need to avoid pregnancy before initiating and during efavirenz therapy.

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/EFV.html).

Pediatric Use: Efavirenz is FDA approved for use as part of combination antiretroviral therapy (cART) in children 3 years or older who weigh at least 10 kg. Limited pharmacokinetic (PK) data in children

younger than age 3 or who weigh less than 13 kg have shown that it is difficult to achieve target trough concentrations in this age group, even with very high (>30 mg/kg) doses of an investigational liquid formulation[1]. Thus, efavirenz is not recommended for use in children younger than age 3 years at this time and no liquid formulation is commercially available. Additional studies are required to determine the appropriate dose of efavirenz in infants and young children. P1070 is an ongoing study collecting data on efavirenz dosing in HIV-infected and HIV/tuberculosis (TB)-coinfected children younger than age 3 years. In addition, efavirenz should be used with caution in adolescent women of childbearing age because of the risk of teratogenicity.

Efavirenz metabolism is controlled by enzymes that are polymorphically expressed and result in large interpatient variability in drug exposure. CYP2B6 is the primary enyzme for efavirenz metabolism, and pediatric patients with the 516 T/T or G/T genotype have reduced metabolism and higher efavirenz levels compared with those with the G/G genotype[2-3]. Additional variant CYP2B6 alleles and variant CYP2A6 alleles have been found to influence efavirenz concentrations in adults[4-5].

Long-term HIV RNA suppression has been associated with maintenance of trough efavirenz concentrations greater than 1 mcg/mL in adults[6]. Early HIV RNA suppression in children has also been seen with higher drug concentrations. Higher efavirenz troughs of 1.9 mcg/mL were seen in subjects with HIV RNA levels less than or equal to 400 copies/mL versus efavirenz troughs of 1.3 mcg/mL in subjects with detectible virus (>400 copies/mL)[7]. In a West African pediatric study, ANRS 12103, early reduction in viral load (by 12 weeks) was greater in children with efavirenz minimum plasma concentration (C_{min}) levels greater than 1.1 mcg/mL or area under the curve (AUC) greater than 51 mcg*h/mL[8]. Even with the use of FDA-approved pediatric dosing, efavirenz concentrations can be suboptimal[2, 8-10]. Therefore , some experts recommend TDM with efavirenz and possibly use of higher doses in young children, especially in select clinical situations such as virologic rebound or lack of response in an adherent patient. In 1 study in which the efavirenz dose was adjusted in response to measurement of the AUC, the median administered efavirenz dose was 13 mg/kg (367 mg/m^2) and the range was from 3 to 23 mg/kg (69–559 mg/m^2)[7]. A PK study in 20 children ages 10 to 16 years treated with the combination of lopinavir/ritonavir 300 mg/m^2 twice daily plus efavirenz 350 mg/m^2 once daily showed adequacy of the lopinavir trough values but suggested that the efavirenz trough was lower than PK targets. The authors therefore recommended that higher doses of efavirenz might be needed when these drugs are used together[11]. TDM can be considered when using efavirenz in combinations with potentially complex drug interactions.

The toxicity profile for efavirenz differs for adults and children. A side effect commonly seen in children is rash, which was reported in up to 40% of children compared with 27% of adults. The rash is usually maculopapular, pruritic, and mild to moderate in severity and rarely requires drug discontinuation. Onset is typically during the first 2 weeks of treatment[12]. Although severe rash and Stevens-Johnson syndrome (SJS) have been reported, they are rare. In adults, CNS symptoms have been reported in more than 50% of patients[13]. These symptoms usually occur early in treatment and rarely require drug discontinuation, but they can sometimes occur or persist for months. Bedtime efavirenz dosing appears to decrease the occurrence and severity of these neuropsychiatric side effects. In several studies, the incidence of such side effects was correlated with efavirenz plasma concentrations and the symptoms occurred more frequently in patients receiving higher concentrations[6, 14-17]. In patients with pre-existing psychiatric conditions, efavirenz should be used cautiously for initial therapy. Adverse CNS effects occurred in 14% of children receiving efavirenz in clinical studies[12] and in 30% of children with efavirenz concentrations greater than 4 mcg/mL[3]. CNS side effects may be harder to detect in children because of the difficulty assessing neurologic symptoms such as impaired concentration, sleep disturbances, or behavior disorders in these patients. TDM can be considered for children with mild or moderate toxicity possibly at-

tributable to a particular ARV agent (see Role of Therapeutic Drug Monitoring in Management of Treatment Failure). In that situation, it is reasonable for the clinician to use TDM to determine if the toxicity is due to an efavirenz concentration in excess of the normal therapeutic range[18-19]. This is the only setting in which dose reduction would be considered appropriate management of drug toxicity and, even then, it should be used with caution.

Efavirenz should be used with caution in adolescent women of childbearing age because of the risk of teratogenicity[20]. See Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health *and* Interventions to Reduce Perinatal HIV Transmission in the United States[21]. Many clinicians choose alternative drugs for use in sexually active adolescent females because of the potential for erratic use of contraception and the high risk of unintended pregnancy.

References

1. Capparelli E, Rochon-Duck M, Robbins B, et al. Age-related pharmacokinetics of efavirenz solution. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections (CROI); February 8-11, 2009; Montréal, Canada. Abstract 884.
2. Saitoh A, Fletcher CV, Brundage R, et al. Efavirenz pharmacokinetics in HIV-1-infected children are associated with CYP2B6-G516T polymorphism. *J Acquir Immune Defic Syndr.* 2007;45(3):280-285.
3. Puthanakit T, Tanpaiboon P, Aurpibul L, et al. Plasma efavirenz concentrations and the association with CYP2B6-516G >T polymorphism in HIV-infected Thai children. *Antivir Ther.* 2009;14(3):315-320.
4. di Iulio J, Fayet A, Arab-Alameddine M, et al. In vivo analysis of efavirenz metabolism in individuals with impaired CYP2A6 function. *Pharmacogenet Genomics.* 2009;19(4):300-309.
5. Arab-Alameddine M, Di Iulio J, Buclin T, et al. Pharmacogenetics-based population pharmacokinetic analysis of efavirenz in HIV-1-infected individuals. *Clin Pharmacol Ther.* 2009;85(5):485-494.
6. Marzolini C, Telenti A, Decosterd LA, et al. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS.* 2001;15(1):71-75.
7. Fletcher CV, Brundage RC, Fenton T, et al. Pharmacokinetics and pharmacodynamics of efavirenz and nelfinavir in HIV-infected children participating in an area-under-the-curve controlled trial. *Clin Pharmacol Ther.* 2008;83(2):300-306.
8. Hirt D, Urien S, Olivier M, et al. Is the recommended dose of efavirenz optimal in young West African human immunodeficiency virus-infected children? *Antimicrob Agents Chemother.* 2009;53(10):4407-4413.
9. Ren Y, Nuttall JJ, Egbers C, et al. High prevalence of subtherapeutic plasma concentrations of efavirenz in children. *J Acquir Immune Defic Syndr.* 2007;45(2):133-136.
10. Viljoen M, Gous H, Kruger HS, et al. Efavirenz plasma concentrations at 1, 3, and 6 months post-antiretroviral therapy initiation in HIV type 1-infected South African children. *AIDS Res Hum Retroviruses.* 2010;26(6):613-619.
11. King JR, Acosta EP, Yogev R, et al. Steady-state pharmacokinetics of lopinavir/ritonavir in combination with efavirenz in human immunodeficiency virus-infected pediatric patients. *Pediatr Infect Dis J.* 2009;28(2):159-161.
12. Starr SE, Fletcher CV, Spector SA, et al. Combination therapy with efavirenz, nelfinavir, and nucleoside reverse-transcriptase inhibitors in children infected with human immunodeficiency virus type 1. Pediatric AIDS Clinical Trials Group 382 Team. *N Engl J Med.* 1999;341(25):1874-1881.
13. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. *N Engl J Med.* 1999;341(25):1865-1873.
14. Gutierrez F, Navarro A, Padilla S, et al. Prediction of neuropsychiatric adverse events associated with long-term efavirenz therapy, using plasma drug level monitoring. *Clin Infect Dis.* 2005;41(11):1648-1653.

15. Zugar A. Studies disagree on frequency of late cns side effects from efavirenz. *AIDS Clin Care.* 2006;4(1).

16. Treisman GJ, Kaplin AI. Neurologic and psychiatric complications of antiretroviral agents. *AIDS.* 2002;16(9):1201-1215.

17. Wintergerst U, Hoffmann F, Jansson A, et al. Antiviral efficacy, tolerability and pharmacokinetics of efavirenz in an unselected cohort of HIV-infected children. *J Antimicrob Chemother.* 2008;61(6):1336-1339.

18. van Luin M, Gras L, Richter C, et al. Efavirenz dose reduction is safe in patients with high plasma concentrations and may prevent efavirenz discontinuations. *J Acquir Immune Defic Syndr.* 2009;52(2):240-245.

19. Acosta EP, Gerber JG. Position paper on therapeutic drug monitoring of antiretroviral agents. *AIDS Res Hum Retroviruses.* 2002;18(12):825-834.

20. Saitoh A, Hull AD, Franklin P, et al. Myelomeningocele in an infant with intrauterine exposure to efavirenz. *J Perinatol.* 2005;25(8):555-556.

21. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. May 24, 2010:1-117. http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf.